AMENDMENTS TO THE CLAIMS

This listing of the claims will replace all prior versions, and listings, of claims in the application:

1 – 240. (Canceled without prejudice).

241. (Currently amended): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual; said fragment or fragments being at least 6 continuous amino acyl residues in length but [[~~less than 110 kDa~~]] of a molecular weight of 140 kDa or less; wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

242. (Currently amended): A method of Claim 241 where the individual referred to in Claim 241 is a first individual and the plasma level referred to [[~~therein~~]] in Claim 241 is [[~~a~~]] the first [[~~individual~~]] individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second [[~~individual's~~]] individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not have neoplastic disease, the plasma level of said fragment or fragments in the

second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) is the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

243. (Canceled without prejudice).

244. (Currently Amended): A method of Claim 241 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing [[~~the~~]] a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by a decrease in said plasma level.

245. (Currently Amended): A method of Claim 241, [[~~242, 243, 244 or 265~~]] 242 or 244 wherein the measurement of a plasma level of a thrombospondin fragment or fragments [[~~level~~]] comprises the use of a binding agent, said binding agent capable of binding said fragment or fragments.

246-247. (Canceled without prejudice).

248. (Currently Amended): A method of Claim [[~~247~~]] 245 wherein the thrombospondin fragment [[~~is~~]] or fragments are separated from thrombospondin before said fragment or fragments are [[~~is~~]] bound to the binding agent.

249. (Currently Amended): A method to detect the presence and/or clinical course of a

neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease; said fragment or fragments being [[~~a~~]] within a molecular weight range selected from the group consisting of 80 to 140 kDa, 40 to 60 kDa, and 20 to 35 kDa [[fragment of claims 1, 2, 3, 4 and/or 5, and/or comprising an epitope therein]] such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

250. (Currently Amended): A method of Claim 249 where the individual referred to in Claim 249 is a first individual and the plasma level referred to [[~~therein~~]] in Claim 249 is [[~~a~~]] the first [[~~individual~~]] individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second [[~~individual's~~]] individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not have neoplastic disease, the plasma level of said fragment or fragments in the second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) [[~~is~~]] in the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

251. (Canceled without prejudice).

252. (Currently Amended): A method of Claim 249 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing [[~~the~~]] a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by a decrease in said plasma level.

253. (Currently amended): A method of Claim 249, [[~~250, 251 or 252~~]] 250 or 252, wherein the measurement of the level of a plasma thrombospondin fragment or fragments [[level]] comprises the use of a binding agent, said binding agent capable of binding said fragment or fragments.

254-255. (Canceled without prejudice).

256. (Currently amended): A method of Claim 253 wherein the thrombospondin fragment or fragments are [[is]] separated from thrombospondin before said fragment or fragment are [[~~is~~]] bound to the binding agent.

257-264 (cancelled without prejudice).

265. (New): A method of Claims 241, 242 or 244 wherein the molecular weight of each of the fragment or fragments is at least 20 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

266. (New): A method of Claim 245 wherein the molecular weight of each of the fragment or fragments is at least 20 kDa, wherein the size in kDa is that determined by gel

electrophoresis after disulfide bond reduction.

267. (New): A method of Claim 248 wherein the molecular weight of each of the fragment or fragments is at least 20 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

268. (New): A method of Claim 245, wherein the binding agent is an antibody.

269. (New): A method of Claim 248, wherein the binding agent is an antibody.

270. (New): A method of Claim 266, wherein the binding agent is an antibody.

271. (New): A method of Claim 267, wherein the binding agent is an antibody.

272 (New): A method of Claim 249, 250 or 252 wherein the molecular weight of the fragment or each of the fragments is within a molecular weight range selected from the group consisting of 85 to 140 kDa fragment, 47 to 53 kDa, and 27 to 33 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

273. (New): A method of Claim 249, 250 or 252 wherein the molecular weight of the fragment or fragments is within a range of 80 to 140 kDa wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

274. (New): A method of Claim 253, wherein the binding agent is an antibody

275. (New): A method of Claim 256, wherein the binding agent is an antibody.

276. (New): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a

neoplastic disease such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual; wherein said fragment or fragments either start between amino acyl residues I-165 and V-263, inclusive, and end between amino acyl residues R-792 and Y-982, inclusive, or is a portion of the range I-165 to Y-982, said portion being at least 150 amino acyl residues in size.

277. (New): A method of Claim 276 where the individual referred to in Claim 276 is a first individual and the plasma level referred to therein is the first individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not have neoplastic disease, the plasma level of said fragment or fragments in the second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) in the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

278. (New): A method of Claim 276 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by

a decrease in said plasma level.

279. (New): A method of Claim 276, 277 or 278 wherein the measurement of a plasma level of a thrombospondin fragment or fragments comprises the use of a binding agent, said binding agent capable of binding said fragment or fragments.

280. (New): A method of Claim 279 wherein the thrombospondin fragment or fragments are separated from thrombospondin before said fragment or fragments are bound to the binding agent.

281. (New): A method of Claims 276 wherein said fragment or fragments further comprising an amino acyl sequence corresponding to SEQ ID NO: 1.

282. (New): A method of Claims 276, 277 or 278 wherein the molecular weight of the portion is at least 20 kDa , wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

283. (New): A method of Claim 279 wherein the molecular weight of the portion is at least 20 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

284. (New): A method of Claim 280 wherein the molecular weight of the portion is at least 20 kDa wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

285. (New): A method of Claim 279, wherein the binding agent is an antibody.

286. (New): A method of Claim 280, wherein the binding agent is an antibody.

287. (New): A method of Claim 283, wherein the binding agent is an antibody.

288. (New): A method of Claim 284, wherein the binding agent is an antibody.

289. (New): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual; the molecular weight of said fragment or any of said fragments not exceeding 140 kDa, the molecular weight of said fragment or fragments being at least 20 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction, and wherein the fragment or each of said fragments comprises a portion of thromobospondin selected from the group consisting of

a collagen type V binding domain, and

a domain or a part thereof within the protease-resistant core of thrombospondin, said domain being selected from the group consisting of a domain of inter-chain disulfide bonds, an oligomerization domain, a procollagen-like domain, a type 1 repeat, a type 2 repeat, and a type 3 repeat.

290. (New): A method of Claim 289 where the individual referred to in Claim 289 is a first individual and the plasma level referred to therein is the first individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not

have neoplastic disease, the plasma level of said fragment or fragments in the second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) in the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

291. (New): A method of Claim 289 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by a decrease in said plasma level.

292. (New): A method of Claim 289, 290 or 291, wherein the measurement of a plasma level of a thrombospondin fragment or fragments comprises the use of a binding agent, said binding agent capable of binding said fragment or fragments.

293. (New): A method of Claim 292 wherein the thrombospondin fragment or fragments are separated from thrombospondin before said fragment or fragments are bound to the binding agent.

294. (New): A method of Claims 289 wherein said fragment or fragments further comprising an amino acyl sequence corresponding to SEQ ID NO: 1.

295. (New): A method of Claim 292, wherein the binding agent is an antibody.

296. (New): A method of Claim 293, wherein the binding agent is an antibody.

297. (New): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual; wherein said plasma level is measured using a binding agent that is capable of binding to said fragment or fragments provided that said binding agent does not bind a region selected from the group consisting of the fibrinogen-binding region in the amino-terminal domain of thrombospondin, and a heparin-binding sequence in the amino-terminal domain of thrombospondin; wherein the molecular weight of each of the fragment or fragments is at least 20 kDa but not more than 140 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

298. (New): A method of Claim 297 where the individual referred to in Claim 297 is a first individual and the plasma level referred to therein is the first individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not have neoplastic disease, the plasma level of said fragment or fragments in the second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) in the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

299. (New): A method of Claim 297 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by a decrease in said plasma level.

300. (New): A method of Claim 297, 298 or 299, wherein the thrombospondin fragment or fragments are separated from thrombospondin before said fragment or fragments are bound to the binding agent.

301. (New): A method of Claim 297, 298 or 299 wherein the binding agent is an antibody.

302. (New): A method of Claim 300, wherein the binding agent is an antibody.

303. (New): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

(1) measuring the individual's plasma level of a thrombospondin fragment or fragments;

(2) utilizing the result of step (1) in a diagnosis as to whether the individual has a neoplastic disease such that the greater the plasma level of said thrombospondin fragment or

fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual; wherein said method comprises the use of a binding agent that binds to an epitope within a plasma fragment in the molecular weight range selected from the group consisting of 80 to 140 kDa, 40 to 60 kDa, and 20 to 35 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

304. (New): A method of Claim 303 where the individual referred to in Claim 303 is a first individual and the plasma level referred to therein is the first individual's plasma fragment level and wherein the method further comprises the steps of:

(3) measuring, in a second individual, the plasma level of the same thrombospondin fragment or fragments measured for the first individual, said second individual considered to not have neoplastic disease, the plasma level of said fragment or fragments in the second individual being the second individual's plasma fragment level;

(4) utilizing the result of step (3) in the diagnosis of whether the first individual has a neoplastic disease such that the greater the extent to which the first individual's plasma fragment level exceeds the second individual's plasma level, the more likely that the diagnosis will be that a neoplastic disease is present in the first individual.

305. (New): A method of Claim 303 further comprising the steps of assaying the individual's plasma level of a thrombospondin fragment or fragments more than once, and utilizing a change in said plasma level from an older to a more recent value to indicate appearance or progression or improvement of a neoplastic disease wherein said appearance or progression is indicated by an increase in the plasma level and said improvement is indicated by

a decrease in said plasma level.

306. (New): A method of Claim 303, 304 or 305 wherein the thrombospondin fragment or fragments are separated from thrombospondin before said fragment or fragments are bound to the binding agent.

307. (New): A method of Claim 303, 304 or 305, wherein the binding agent is an antibody.

308. (New): A method of Claim 306, wherein the binding agent is an antibody.

309. (New): A method to detect the presence and/or clinical course of a neoplastic disease in an individual, wherein the method comprises the steps of:

1) utilizing a first binding agent to obtain a quantification of a total, thrombospondin plus either the thrombospondin fragment or fragments;

2) utilizing a second binding agent, to obtain a quantification of thrombospondin only;

3) utilizing the difference between the quantifications obtained in steps (1) and (2) as a quantitation of the amount of thrombospondin fragment or fragments; and

4) utilizing the result of step (3) in a diagnosis as to whether the individual has a neoplastic disease such that the greater the plasma level of said thrombospondin fragment or fragments, the more likely that the diagnosis will be that a neoplastic disease is present in said individual;

wherein the first binding agent binds to an epitope shared by thrombospondin and the thrombospondin fragment or fragments, and wherein the second binding agent binds to an epitope present in thrombospondin but not present in the fragment or fragments.

310. (New): A method of Claim 309 wherein said fragment or fragments are at least 6 continuous amino acyl residues in length but of a molecular weight of 140 kDa or less; wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

311. (New): A method of Claim 309 wherein said fragment or fragments are within a molecular weight range selected from the group consisting of 80 to 140 kDa, 40 to 60 kDa, and 20 to 35 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

312. (New): A method of Claim 309 wherein wherein said fragment or fragments either start between amino acyl residues I-165 and V-263, inclusive, and end between amino acyl residues R-792 and Y-982, inclusive, or is a portion of the range I-165 to Y-982, said portion being at least 150 amino acyl residues in size.

313. (New): A method of Claim 309 wherein the molecular weight of said fragment or any of said fragments not exceeding 140 kDa, the molecular weight of said fragment or fragments being at least 20 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction, and wherein the fragment or each of said fragments comprises a portion of thromobospondin selected from the group consisting of

a collagen type V binding domain, and

a domain or a part thereof within the protease-resistant core of thrombospondin, said domain being selected from the group consisting of a domain of inter-chain disulfide bonds, an oligomerization domain, a procollagen-like domain, a type 1 repeat, a type 2 repeat, and a type 3 repeat.

314. (New): A method of Claim 309 wherein said first binding agent does not bind a region selected from the group consisting of the fibrinogen-binding region in the amino-terminal domain of thrombospondin, and a heparin-binding sequence in the amino-terminal domain of thrombospondin; wherein the molecular weight of each of the fragment or fragments is at least 20 kDa but not more than 140 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

315. (New): A method of Claim 309 wherein said first binding agent binds to an epitope within a plasma fragment in the molecular weight range selected from the group consisting of 80 to 140 kDa, 40 to 60 kDa, and 20 to 35 kDa, wherein the size in kDa is that determined by gel electrophoresis after disulfide bond reduction.

316. (New): A method of Claim 309, 310, 311, 312, 313, 314 or 315 wherein one or both of said first and second binding agents is an antibody.